

Atty. Dkt. No. B-0459 US

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AMENDMENTS TO THE CLAIMS

The complete listing of all claims will serve to replace all prior versions of the claims. Applicants respectfully request favorable consideration of the present application in light of the present remarks.

Listing of claims

1. (currently amended) A MRI detectable species according to formula (I) which upon contact with the cells or cell surfaces of a human or other animal is incorporated into or onto the animal's cells or cell surfaces and which provides contrast sufficient to clearly distinguish between normal, healthy cells and tumor cells, wherein;



D is a MRI detectable moiety selected from the group consisting of coated ferromagnetic particles, coated superparamagnetic particles and chelated complexes of paramagnetic metal ions;

S is a spacer;

N is a molecule of a nutrient or pseudo-nutrient ~~comprising monosaccharides, essential amino acids and their derivatives, polyamines and non-essential amino acids~~ selected from alanine, phenylalanine, lysine, arginine, putrescine, spermidine, spermine, asparagine, agmatine and glutamine and n is an integer of 0 to 5, m is an integer of 1 to 5 and p is an integer of 1 to 10.

2. (previously presented) The MRI detectable species of claim 1 wherein D contains at least one site for attachment to the spacer S or the nutrient/pseudo-nutrient molecule N.
3. (previously presented) The MRI detectable species of claim 1, wherein the moiety D is a chelated complex of a paramagnetic metal ion selected from the ions of transition and lanthanide metals with a chelating ligand L.
4. (original) The MRI detectable species of claim 3, wherein the paramagnetic metal ion is selected from the ions having atomic number of 21 to 29, 42, 43, 44, or 57 to 71, and the chelating ligand L is selected from the group consisting of the residue of a polyaminopolycarboxylic acid, either linear or cyclic, in racemic or optically active form, such as ethylenediaminetetracetic acid (EDTA), diethylenetriaminopentaacetic acid (DTPA), N-[2-[bis(carboxymethyl)-amino]-3-(4-

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ethoxyphenyl)propyl]-N-[2-[bis(carboxymethyl)amino]ethyl]-L-glycine (EOB-DTPA), N,N-bis[2-[bis(carboxymethyl)amino]ethyl]-L-glutamic acid (DTPA-GLU), N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-L- γ -glutamyl-L-glutamine, N,N-bis[2-[bis(carboxymethyl)amino]ethyl]-L-lysine (DTPA-LYS), the DTPA mono- or bis-amide derivatives, such as N,N-bis[2-[carboxymethyl[(methylcarbonyl)-methyl]amino]ethyl] glycine (DTPA-BMA), 4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oic acid (BOPTA), 1,4,7,10-tetraazacyclo-dodecan-1,4,7,10-tetraacetic acid (DOTA), 1,4,7,10-tetraazacyclododecan-1,4,7-triacetic acid (DO3A), 10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecan-1,4,7-triacetic acid (HPDO3A), 2-methyl-1,4,7,10-tetraazacyclododecan-1,4,7,10-tetraacetic acid (MCTA), ($\alpha,\alpha',\alpha'',\alpha'''$)-tetramethyl-1,4,7,10-tetraazacyclododecan-1,4,7,10-tetraacetic acid (DOTMA), 3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid (PCTA), [4-(1,6,10-triazaundecan)-phenyl-aminocarbonylmethyl]-1,4,7,10-tetraazacyclododecan-4,7,10-triacetic acid; a derivative thereof wherein one or more of the carboxylic groups are in the form of the corresponding salts, esters, or amides; and the residue of a corresponding compound wherein one or more of the carboxylic groups is replaced by a phosphonic and/or phosphinic group, such as for instance 4-carboxy-5,11-bis(carboxy-methyl)-1-phenyl-12-[(phenylmethoxy)methyl]-8-(phosphonomethyl)-2-oxa-5,8,11-triazatridecan-13-oic acid, N,N'-[(phosphonomethylimino)di-2,1-ethanediyl]bis[N-(carboxymethyl)glycine], N,N'-[(phosphonomethylimino)di-2,1-ethanediyl]bis[N-(phosphonomethyl)glycine], N,N'-[(phosphinomethylimino)di-2,1-ethanediyl]bis[N-(carboxymethyl)glycine], 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis[methylen(methylphosphonic)]acid, or 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrakis[methylen(methylphosphinic)]acid.

5. (previously presented) The MRI detectable species of claim 3 wherein the complex is formed with a metal ion selected from the group consisting of Mn, Fe, Eu, Gd and Dy.
6. (cancelled)
7. (previously presented) The MRI detectable species of claim 1 wherein the spacer S, if present, is a homo- or hetero-bifunctional linker where the two reactive moieties are separated by alkylidene, alkenylidene, alkynylidene, cycloalkylidene arylidene, or aralkylidene radical that can be substituted and can be interrupted by heteroatoms such as oxygen, nitrogen, and sulphur.
8. (original) The MRI detectable species of formula (I) according to claim 7, wherein the reactive moieties are separated by an aliphatic, straight or branched chain, that may be interrupted by -O-, -S-, -CO-, -NR-, -CS- and the like groups or by aromatic rings, and may be an -OR-, -SR-, -NRR₁,

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-COOR, -CONRR₁, and the like substituents, wherein R and R₁, each independently, may be a hydrogen atom or an organic group.

9. (previously presented) A process for the preparation of a the MRI detectable species of claim 1, said process comprising:

- conjugating the spacer S, if any, with the nutrient or pseudo-nutrient molecule N, and the thus obtained intermediate with the MRI detectable moiety D or a precursor thereof; or
- conjugating the MRI detectable moiety D or a precursor thereof with the spacer S, if any, and the thus obtained intermediate with the nutrient or pseudo-nutrient molecule N; and

when a precursor of the MRI detectable moiety D is used, converting said precursor into the desired MRI detectable moiety.

10. (cancelled).

11. (currently amended) An intermediate compound of formula (II)



wherein L is a chelating ligand;

S is a spacer,

N is a molecule of a nutrient or pseudo-nutrient comprising

~~monosaccharides, essential amino acids and their derivatives, polyamines and non-~~
essential amino acids selected from alanine, phenylalanine, lysine, arginine, putrescine, spermidine, spermine, asparagine, agmatine and glutamine; and

n is an integer of 0 to 5;

m is an integer of 1 to 5; and

p is an integer of 1 to 10.

12. (currently amended) A compound according to Claim 11 selected from the group consisting of:

6,16-dicarbonyl-5,8,11,14,17-pentaaza-8,11,14-tricarboxymethyl-heneicosandiguadinine;

6,16-dicarbonyl-5,19-dicarboxy-5,8,11,14,17-pentaaza-8,11,14-tricarboxymethyl-heneicosandioic acid diamide;

3,6,9-triaza-3,6,9-tricarboxymethylundecanoic acid bis-glucopyranosylamide;

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2,24-diamino-8,18-dicarbonyl-7,10,13,16,19-pentaaza-10,13,16-tricarboxymethyl-pentaheicosandioic acid;

2,16-dibenzyl-4,13-dicarbonyl-3,6,9,12,15-pentaaza-6,9,12-tricarboxymethyl-heptadecandioic acid;
10,20-dicarbonyl-4,9,12,15,18,21,26-heptaaza-12,15,18-tricarboxymethyl-nonaheicosan-1,29-diamine;

4,26-diamino-5,10,20,25-tetracarbonyl-12,15,18-tricarboxymethyl-6,9,12,15,18,21,24-heptaaza-nonaheicosan-1,29-diguanidin[[a]]c;

N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-L-γ-glutamyl-L-glutamine;

N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-L-γ-glutamyl-argmatine;

N,N-Bis[2-[bis(carboxymethyl)amino]ethyl]-L-γ-glutamyl-arginine; and

[4-(1,6,10-triazaundecan)-phenyl-aminocarbonylmetl]-1,4,7,10-tetraazacyclododecan-4,7,10-triacetic acid.

13. (previously presented) A pharmaceutical composition comprising a MRI detectable species of any one of claims 1 to 5 in an amount sufficient to give the desired level of contrast and at least one pharmaceutically acceptable carrier.

14-16 (cancelled).

17. (previously presented) A method imaging organs and/or tissues of an animal, comprising administering a composition comprising a the MRI detectable species of any one of claims 1 to 5 and imaging the organs and/or tissues using nuclear magnetic resonance.

18. (previously presented) A method of diagnosing tumors in an animal, comprising administering a composition comprising the MRI detectable species of any one of claims 1 to 5 and imaging the animal using nuclear magnetic resonance.

19. (currently amended) A process for the preparation of a MRI detectable species of formula (I)



Wherein D is a MRI detectable moiety selected from the group consisting of coated ferromagnetic particles, coated superparamagnetic particles and chelated complexes of paramagnetic metal ions;

S is a spacer;

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N is a molecule of a nutrient or pseudo-nutrient comprising ~~monosaccharides, essential amino acids and their derivatives, polyamines and non-essential amino acids~~ selected from alanine, phenylalanine, lysine, arginine, putrescine, spermidine, spermine, asparagine, agmatine and glutamine;

n is an integer of 0 to 5;

m is an integer of 1 to 5; and

p is an integer of 1 to 10;

wherein the process comprises preparing an intermediate of claim 11 and converting said intermediate into the desired end compound of formula (I) by metallation with a suitably selected paramagnetic metal ion.